UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,618	02/22/2002	Alan D. Olstein	7005-0003	4458

23980 7590 07/28/2004

REED & EBERLE LLP
800 MENLO AVENUE, SUITE 210
MENLO PARK, CA 94025

EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,618	OLSTEIN ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8 and 65-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8 and 65-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

1. Currently claims 1-3, 8, and 65-67 are pending and under consideration in the application to the extent that they read on the elected invention, wherein the conjugate comprises the bacteriocin nisin. In the prior action, mailed on January 28, 2004, claims 1-4, 6-9, and 64-67 were rejected, and claims 5, 10-63, and 68-72 stood withdrawn as to non-elected inventions. In the Response filed on June 28, 2004, the Applicant amended claims 1, 8, and 65-67, and cancelled claims 4-7, 9-64, and 68-72.

2. Claims 1-3, 8, and 65, which read on the elected invention, appear to be allowable to the extent that they read on the elected invention. It is noted that claims 1-3 read on non-elected subject matter: i.e. embodiments wherein the bacteriocin is a peptide other than nisin or the nisin precursor. Cancellation of the non-elected subject matter is required before the claims will be allowed.

3. Because this Office action raises new grounds of rejection not necessitated by amendment, this action is made Non-Final.

Specification

4. **(Prior Objection- Withdrawn)** The disclosure was objected to because of the following informalities: on page 42, lines 25-26, the discussion of Example 3 refereed to "the Nisin-Co (II) complex (of Example 3)." In view of the amendment to the specification, the objection is withdrawn.

Sequence Listing

(Prior objection-withdrawn) This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). The sequence listing was objected to in the prior action. In view of the submission of the corrected listing, the objection is withdrawn.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. **(Prior Rejection- Withdrawn)** Claims 1-4, 6-9, and 64-68 were rejected in the prior action under 35 U.S.C. 101 for reading on non-statutory subject matter. These claims read on chelated complexes of nisin and cobalt in an in vitro sample to be tested. Claims 4, 6, 7, 9, 64, and 68 have been cancelled from the application. The remaining claims have been amended to read on embodiments wherein nisin complexes with cobalt. While the art, as described below, indicates that nisin, through its lanthionine molecules, would be capable of binding cobalt, there is no indication that the peptide actually binds to cobalt in nature. The rejection is therefore withdrawn.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. **(Prior Rejection- Withdrawn)** Claim 65 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite because there was no definition in the specification as to what hybridization conditions the Applicant considers to be "stringent." In view of the cancellation of the rejected language from the claim, the rejection is withdrawn.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. **(Prior Rejection- Withdrawn)** Claim 65 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for complexes of a bacteriocin of SEQ ID NO: 8 and a metal, is not enabling for complexes comprising bacteriocins that hybridize under stringent conditions to SEQ ID NO: 8. In view of the amendment of the claim, the rejection is withdrawn.

11. **(Prior Rejection- Maintained)** Claims 1-4, 6- 9, and 64- 67 were rejected in the prior action under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims were rejected as lacking sufficient written description support for the claims to the extent that they read on conjugates comprising fragments, homologs, and variants of bacteriocins and a transitional metal. In view of the cancellation of the rejected subject matter

from claims 1-3, 8, and 65, and the cancellation of claims 6, 7, 9, and 64 from the application, the rejection is withdrawn from these claims.

However, each of claims 66 and 67 still read on the rejected embodiments. As no arguments in traversal or evidence of enablement have been provided, the rejection is maintained against these claims.

12. **(Prior Rejection- Maintained)** Claims 1-4, 6-9, and 64-67 were rejected in the prior action under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for complexes comprising a bacteriocin and a transition metal, does not reasonably provide enablement for complexes comprising bacteriocin variants and transition metals. The claims were rejected as lacking sufficient enabling support for the claims to the extent that they read on conjugates comprising fragments, homologs, and variants of bacteriocins and a transitional metal. In view of the cancellation of the rejected subject matter from claims 1-3, 8, and 65, and the cancellation of claims 6, 7, 9, and 64 from the application, the rejection is withdrawn from these claims.

However, each of claims 66 and 67 still read on the rejected embodiments. As no arguments in traversal or evidence of enablement have been provided, the rejection is maintained against these claims.

13. **(New Rejection)** Claims 65-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed invention wherein the peptide is the mature form of nisin, does not reasonably provide enablement for embodiments wherein the

peptide comprises the full length sequence of SEQ ID NO: 5 or of the sequence encoded by SEQ ID NO: 8. These sequences represent the full-length sequence of the precursor protein to nisin. See, App., page 10. The claims read on any sequence from within the precursor sequences disclosed as SEQ ID NO: 5, or encoded by SEQ ID NO: 8. Thus, the claims read on the claimed conjugate of the pre-nisin protein and cobalt, or any sequence within these polypeptides.

The factors to be considered when making a determination as to whether a claim is enabled have been identified in the prior actions. See e.g., action mailed on July 28, 2003, pages 5-6. In the present case, these factors favor a finding that the Applicant has not provided an enabling description for the claims described above.

The claims are rejected for two reasons. First, the Applicant is not enabled for embodiments wherein the claimed complex comprises the full-length sequences of the precursor protein. Second, the Applicant is not enabled for complexes comprising any sequence within the precursor sequence other than the mature form of nisin.

While the claims describe a conjugate comprising the any sequence within the nisin precursor and cobalt, there are no working examples of conjugates of either the full-length precursor, or non-mature form peptides provided in the specification. It is noted that the application does disclose a working example comprising nisin and cobalt (pages 41-43). However, such is not found sufficient to also demonstrate enablement of embodiments using the precursor protein. This is because, as was described in the prior actions, the claimed conjugates require two functional characteristics in order to operate. First, the peptides must be capable of binding to the metal. Second, the peptide must also be capable of binding to a target bacterium.

The distinction between nisin and its precursor is based on the teachings of the art with reference to the latter of these two functions.

With respect to the first grounds of rejection, it appears that the metal binding activity of nisin is maintained by the nisin precursor. This is evidenced by the teachings of Surovoy et al. (of record in the action mailed on January 28, 2004). Surovoy teaches that the precursor to nisin is known to interact with both zinc and copper. Page 564. Thus, the precursor protein would appear to have the first of the two required functions.

However, in addition to the metal binding activity, the peptides are also required to be capable of binding to the target bacterium. But, whereas the art teaches that the metal binding activity is likely to be possessed by the precursor, the art also indicates that the antimicrobial functions of nisin are not inherent to that protein. For example, page 59 of the Sahl and Beirbaum reference (of record in the IDS of May 2002) teaches that removal of the precursor leader sequence is required to activate the bacteriocin. Further, Jung et al. (Angew Chem Int Ed Eng 30: 1051-68) teaches on page 1055 that two rings found in the modified mature form of nisin are required for the peptide to function. Thus, because the precursor protein of SEQ ID NO: 5 both comprises the leader sequence, and does not comprise the required rings in its conformational structure, and therefore is unlikely to have the required antimicrobial or microbe binding activity required by the claimed conjugate, it would appear that the precursor protein would not be an effective protein for use in the claimed invention. The Applicant is therefore not enabled for the claimed invention to the extent that it reads on conjugates of the nisin precursor of SEQ ID NO: 5.

It is noted that a comparison of SEQ ID NO: 8 to SEQ ID NO: 5 indicates that the peptide encoded by residues 297-468 of SEQ ID NO: 8 differs from the sequence of SEQ ID NO: 5 by a single residue at position 27. In view of the close similarity between the sequences, and the fact that both are asserted to be nisin encoding, or pre-nisin sequences, and the teachings described above with respect to SEQ ID NO: 5, those in the art would have assumed that those teachings would also apply to the peptide encoded by SEQ ID NO: 8. Those in the art would therefore also not have expected the full sequence encoded by SEQ ID NO: 8 to operate in the claimed invention for the same reasons as indicated with respect to SEQ ID NO: 5.

The second ground of rejection is concerned with the claims as they describe embodiments of the claimed invention wherein the claimed complex comprises a peptide comprising any amino acid sequence within SEQ ID NO: 5 or encoded by SEQ ID NO: 8. As was indicated above, these sequences are precursor proteins to nisin. The precursors include the leader sequence, which is cleaved off the peptide to activate it. See, Sahl and Beirbaum, supra. However, neither the art, nor the application has provided any evidence that this sequence has either of the required functional characteristics for operation in the claimed invention. Because the application has not demonstrated that any peptide from the precursor protein, other than the mature form of nisin, would be operative in the claimed invention, and because the art provides teachings suggesting that only the mature form would be operative, the claims are rejected for exceeding the scope of enablement.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. **(Prior Rejection- Withdrawn)** Claims 1-4, and 7 were rejected under 35 U.S.C. 102(b) as being anticipated by Pommer et al., J Biol Chem, supra. The claims read on chelated complexes comprising a bacteriocin, and a transitional metal, including embodiments wherein the metal is Cobalt. However, the claims have now been amended such that they no longer read on the conjugate disclosed by Pommer (wherein the bacteriocin is colicin). This rejection is therefore withdrawn.

16. **(Prior Rejection- Withdrawn)** Claims 1-4, 6, 8, 64-67 were rejected under 35 U.S.C. 102(b) as being anticipated by Surovoy et al. (supra). These claims have been described above, except that the claims have also been amended to require that the conjugate comprises the metal cobalt. Because the reference does not teach embodiments wherein the pre-nisin sequence binds to cobalt, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. **(Prior Rejection- Reformed and Maintained)** Claims 1-4, 6-9, and 64 were rejected under 35 U.S.C. 103(a) as being unpatentable over Siddigi et al. (U.S. Patent 5,541,113), in view of Olstein et al., (U.S. Patent 5,750,357), Meyer et al. (Arch Microbiol 167:67-77), and Friedman (J Agricult Food Chem 47(4): 1295-319). For the reasons below, the rejection is reformed as a rejection of claims 1-3, 8, and 65 over the teachings of Siddigi in view of Olstein, Meyer, and Pearce et al. (J Agric Food Chem 36: 7070-17). For the purposes of this rejection, claim 65 is read as including the mature form of the nisin peptide encoded by SEQ ID NO: 8.

Applicant has amended to claims to require that the metal is cobalt, and by inserting the limitations of claim 6 into claim 1. The Applicant argues that this amendment avoids the prior art rejection. This argument is not found persuasive. As was indicated in the prior action, the rejection was restated such that claims 1-4, 6-9, and 64 were rejected over the new combination of references.

However, the Applicant has presented further arguments with respect to the teachings of Siddigi, Meyer, and Friedman in response to the rejection of claims 1-5, 6-9, and 64-67 Siddigi in view of Olstein, Meyer, and Friedman as applied above, further in view of Buchman. In particular, the Applicant asserts that none of the references provide teachings regarding the binding of cobalt by nisin. Whereas the Fried man reference specifically provides teachings regarding the metal binding properties of lysinoalanine (LAL), the reference does not refer to the metal binding properties of nisin, or the lanthionine amino acid structure contained by the peptide. This argument is found persuasive.

However, while the teachings of Friedman fail to suggest that nisin would have the same binding properties as the LAL containing peptides, such a suggestion is present in the teachings

of Pearce. This reference indicates that lanthionine (LAN) has similar metal binding properties to LAL. See, abstract, pages 713. These teachings, particularly when seen in combination with the teachings of Friedman, which suggests that these cross-linked amino acids share certain properties), and with Surovoy (teaching the affinity for nisin and prenisin for zinc), and Weber (Int J Protein Res 3:225-59- teaching affinity between LAN and copper), would have suggested to those in the art that nisin, which comprising LAN, would also bind cobalt. The rejection, as reformed, is therefore maintained.

19. **(Prior Rejection- Reformed and Maintained)** Claims 66 and 67 were rejected under 35 U.S.C. 103(a) as being unpatentable over Siddigi in view of Olstein, Meyer, and Friedman, and further in view of Gasson. The Applicant argues that the rejection is overcome in view of the amendment of claim 1 such that it incorporates the limitations of claim 6. This rejection is reformed and maintained for the reasons indicated above such that claims 66 and 67 are rejected (to the extent that they read on complexes comprising the mature form of the nisin protein) over the teachings of Siddigi in view of Olstein, Meyer, and Pearce.

20. **(Prior Rejection- Reformed and Maintained)** Claims 1-5, 6-9, and 64-67 were rejected as obvious over the teachings of Siddigi in view of Olstein, Meyer, and Friedman as applied above, further in view of Buchman et al. (J Biol Chem 263(31): 16260-66). The claims have been described in the prior actions. This rejection is reformed and maintained for the reasons indicated above and of record such that claims 1-3, 8, and 64-67 are rejected (to the extent that

they read on complexes comprising the mature form of the nisin protein) over the teachings of Siddigi in view of Olstein, Meyer, and Pearce and further in view of Buchman.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

James C. Housel 7/26/04

JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600